UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,373	05/16/2001	Robert P. Kimberly	UAB-14202/22	5348

7590 05/07/2004

EXAMINER
SAKELARIS, SALLY A

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/07/2004

Ellen S Cogen
Gifford Krass Groh Sprinkle Anderson & Citkowski
Suite 400
280 N Old Woodward Avenue
Birmingham, MI 48009-5394

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,373	KIMBERLY, ROBERT P.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30,34 and 36-46* is/are pending in the application.

4a) Of the above claim(s) *22-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21, 26-30, 34, and 36-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 3/3/2004 and 12/29/2003 have been entered. Claims 1-21, 26-30, 34, and 36-46 are examined herein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

1. Claim 34 is rejected under 35 U.S.C. 102(e) as being anticipated by Chee et al.(US Patent 5,856,104)

Chee et al. teach a commercial package and/or a reagent kit, comprising reagents for the PCR based detection of polymorphisms and further teach the accompaniment of "instructions for carrying out the methods."(Col. 13)

Response to Arguments:

Applicant's traversal on the grounds that, the Chee et al. reference is "incapable of performing the functions of pending claim 34" is acknowledged but the examiner maintains her position that the reference does anticipate this claim's recitation of the intended use that does not result in a structural difference between the claimed invention and the prior art. Applicant should note that in fact the Chee et al. reference does anticipate claim 34 as the claim as presently written does not require the identification of the specific SNP in a FcαRI genotype or phenotype. In response to applicant's argument that claim 34 is not anticipated, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-21 and 26-30, 34, and 36-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of the invention. Claims 1-21, 26-30, 34, and 36-46 are broadly drawn to methods of correlating the ability of a cell expressing FcαRI to bind IgA and cellular susceptibility to a disease. The specification does not at all enable correlating the ability of a cell expressing FcαRI to bind IgA and cellular susceptibility to any disease by identifying a FcαRI genotype of said cell for FcαRI alleles selected from the group consisting of: FcαRIa 87R/87R, FcαRIA 92D/92N, FcαRIa 132F/132L, FcαRI 245P/245L and FcαRI 248S/248G. The specification does not specify any examples of such well-established, *in–vitro* model systems or evidence for the ability of a cell's receptors expressing FcαRI to bind IgA and its predictable association with cellular susceptibility to any disease. The examples that are taught in the specification include only SNPs in the coding regions of FcγRIIA, FcγRIIIA, and FcγRIIIB and a belief that a "precedent" is established by these findings, that these SNPs influence the risk for Periodontal Disease(PD).

The specification continues on to conclude that the findings for one gene coding for the IgG receptor can be applicable to that of another gene coding for the different, IgA receptor. The specification teaches that the "knowledge that PD lesions are rich in both IgG and IgA."(Pg 23, line 20-23) is enough to lead one skilled in the art to believe that their receptors function exactly the same. The specification merely prophesizes that as a result of these previous findings with the IgG receptor, "the present invention identifies novel SNPs in FcαRI." It is highly unpredictable to extrapolate findings from the Fcγ molecules to the entirely different molecules defined by FcαRI. In addition, it is important to note that even if applicant would enable the detection of SNPs in the FcαRI gene, only those genotypes taught in the specification on Pg. 33 in example 3, would be enabled, not all genotypes of the receptor. Furthermore, this method includes i). identifying a FcαRI genotype from the group consisting of 87R/87R, FcαRIA 92D/92N, FcαRIa 132F/132L, FcαRI 245P/245L and FcαRI 248S/248G, ii). quantifying IgA binding by a cell with said genotype, and iii). comparing IgA binding by said cell and IgA binding by a second cell, said second cell expressing a second FcαRI genotype. Furthermore, while the method's step i), of identifying a genotype would include the "how to make" portion of the enablement requirement, it still omits the "how to use portion" as the specification omits any teaching of how to use the discovered genotype once it has been discovered. With respect to step ii), it is unclear how the amount of bound IgA relates to the genotype of a cell. The specification does not teach the effect that the amount of bound IgA has on the genotype of the cell or vice versa. Lastly, as in steps i) and ii), the specification does not teach which genotype said first cell has nor what genotype said second cell has and why either of these would be significant as related to each cell's ability to bind IgA.

With respect to claim 34, although directed to a product, the reagents will be used to identify individual susceptibility to a disease, a feat that as previously mentioned lacks enablement because of the great unpredictability that exists in such a research project. The nature of this invention is quite unpredictable because it requires a reliance on the prophetic testimony by applicant that the progression of any disease will in fact be evident through the detection of any FcαRI genotype selected from the group consisting of 87R/87R, FcαRIA 92D/92N, FcαRIa 132F/132L, FcαRI 245P/245L and FcαRI 248S/248G.

Scope of the invention. The scope of the invention is very broad, claiming methods for correlating the ability of any type of cell expressing FcαRI to bind IgA and the cellular susceptibility to any disease. Much unpredictability exists in the broad claiming of any type of cell and having, as in steps i) ii) and iii)'s, any genotype selected from the group consisting of 87R/87R, FcαRIA 92D/92N, FcαRIa 132F/132L, FcαRI 245P/245L and FcαRI 248S/248G being correlated to any amount of bound IgA by the cell expressing said genotype. Furthermore, as eluded to in the Nature of the invention, even if applicants would enable detection of SNPs in the FcαRI gene, their scope would still be limited to those delineated in example 3 of the specification.

State of the art. The prior art does not disclose a method for correlating the ability of a cell expressing FcαRI to bind IgA and cellular susceptibility to a disease, thus the invention appears to be novel in terms of the prior art. However, the lack of support from the prior art for the ability of a genotype of the FcαRI, IgA receptor, to have such far-reaching effects such as into the manifestation of any disease, results in the invention being unpredictable in terms of its use as presently claimed. Furthermore, as the present application relies on the extrapolation from data involving the receptor for the IgG molecule to define characteristics for the receptor of the IgA molecule, the art teaches great unpredictability associated with this practice. The

specification's reliance on the IgG receptor data implies that IgG and IgA are identical. However, Morton et al. teach "the cDNA encoding the myeloid FcαR has been characterized and was found to encode a 30-kDa peptide with two extracellular Ig-like domains" the reference goes on to teach though that, "the gene structure indicates FcαR to represent a more distantly related member of the immunoglobulin receptor gene family." (JBC, 1995) Furthermore, Carayannopoulos et al. teach while the FcαR receptor "shows similarity to the high affinity FcεR and the three FcγR but is more distantly related to these receptors than they are to one another"(J. Exp. Med. 1996). In addition to the prior art, the post date art also teaches variation between these two receptor types. Wines et al teach that the "comparison of the FcγRI:IgA interaction showed considerable differences from the well-defined FcγR:IgG and FcεRI:IgE interactions. Unlike other Fc receptors, in FcαRI the ligand binding site appears to be in the first domain, not the second, and in IgA, unlike IgG or IgE, the receptor binding site is located at the interface between CH2 and CH3, not the lower hinge of CH2 as for IgG or its equivalent area in IgE Cε2."(AAI, 2001) Such variance between IgG receptors and those for IgA makes drawing conclusions and the subsequent extrapolations about the two molecules, highly unpredictable.

Furthermore, with respect to the applicant's assertion that their invention provides SNPs that "lead to coding changes in both the extracellular and cytoplasmic domains"(Spec. pg. 8) and that "the present invention uses a single nucleotide polymorphism or combinations thereof within a FcαRI genotype to identify individual susceptibility to a disease"(Pg. 9), the prior art does not provide any specific guidance with regard to the instantly claimed particular polymorphism located in FcαRI. There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell

anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

Determining how to use the claimed polynucleotides as asserted by applicant, for example for the diagnosis of disease, requires the knowledge of unpredictable and potentially non-existent associations between the polymorphism and some periodontal disease or other disease state. Even if the elected polymorphism is in some way associated with some disease state, it is difficult (if not impossible) to know or predict from the teachings of the specification which disease or how the polymorphism(and what polymorphism) is associated. That is, it is unpredictable as to whether the presence of a particular allele the polymorphism would confer a higher or lower likelihood of having the disease. In this case, the possible uses for the claimed methods are undefined, beyond the suggestion that they can be used to detect a disease associated with the polymorphism.

Number of working examples and Guidance provided by applicant. The instant specification only provides guidance and working examples concerning the FcγRI, RIIA, RIIIA, and RIIIB IgG receptor molecules. Considering the unpredictability surrounding the extrapolation of data from experiments using different receptor molecules, as pointed out in the Nature of the invention section of this rejection, the skilled artisan would have to practice undue and unpredictable trial and error experimentation in order to practice the invention with the

genotypes of IgA receptors(FcαRI) that are not the genotypes of IgG receptors(FcγRI..etc.). In addition, considering the lack of working examples showing the association between a particular SNP and a specific disease, even more unpredictability exists.

Level of skill in the art. The level of skill involved in relating characteristics of such different molecules(FcαRI and FcγRI etc) to each other is very high if not impossible. Additionally, the functional use of such assumed similar properties from such different molecules is seen, in this instance, to be prophetic.

Unpredictability of the art. There are examples of differences in the IgG receptor and that being claimed, the IgA as illustrated in the State of the Art section. Both the prior art and the instant specification are deficient in terms of teaching the applicability of IgG receptor data to that of IgA genotype effects. Furthermore, the lack of teachings of how to use any genotype selected from the group consisting of 87R/87R, FcαRIA 92D/92N, FcαRIa 132F/132L, FcαRI 245P/245L and FcαRI 248S/248G of the FcαRI gene, and also how the amount of IgA binding relates to this genotype both contribute to the great unpredictability involved in making and using this invention. In light of these deficiencies, the skilled artisan would be forced to practice undue and unpredictable trial and error experimentation when practicing the instant invention.

Considering the Nature of the invention, the guidance provided by both the prior art and the instant specification, and the broad scope of the invention, it is clear that the skilled artisan would be required to practice undue and unpredictable trial and error experimentation to practice the invention that is claimed.

Response to Arguments:

Applicants assert on page 12 of their response that the "Examiner's concern that the specification lacks evidence as to the ability of FcαRI is contrary to the knowledge of one of skill

in the art at the time the invention was made". First, applicant should note that the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. Second, even if the references cited teach a role of IgA binding affinity in periodontal disease, that is not what the examiner asserted to be missing from the specification. It is the absence of any correlation between the ability of a cell expressing FcαRI to bind IgA and cellular susceptibility to any disease through the detection of a genotype from the group consisting of 87R/87R, FcαRIA 92D/92N, FcαRIa 132F/132L, FcαRI 245P/245L and FcαRI 248S/248G that is responsible for the unpredictability involved in the present invention.

With respect to the subsequent arguments concerning the maintained rejection under 35 U.S.C. 112, first paragraph, the examiner acknowledges applicant's assertion; that the in re Wands factors are satisfied by the instant specification, that with a finding of enablement for each and every element of the claimed invention the resulting invention is enabled, and further that they assert that "it is not necessary that a court review all the Wands factors to find a disclosure enabling. These arguments are not found to be convincing. The examiner acknowledges that while a whole method may be not enabled, its constitutive steps may. For example, a method that is drawn to a cure for all cancers that comprises the detection of SNPs is clearly not enabled whilst the single method step of SNP detection is clearly enabled by both prior and post date art and one of ordinary skill in the art. As a result, the examiner finds applicants arguments on pages 11-12 to be unconvincing. On page 11 applicant analyzes each method step and points the examiner to the relevant lines within the specification that alledgedly enable each step. Applicant's analysis of the method steps is acknowledged, however, the enablement for the method as claimed, ie the correlation of the ability of a cell expressing FcαRI to bind IgA and cellular susceptibility to a disease cannot be found by analyzing each step individually since while each step may be enabled, the method in its entirety is not.

Additionally, as mentioned above, applicants point examiner(on page 12) to references 45-50 that "explicitly identify a role if IgA binding affinity in periodontal disease. Even if

arguendo, these references teach "a role of IgA binding affinity in periodontal disease", the references still lack a teaching that is capable of enabling the claims as broadly as they are presently written, which is to say to for example to all diseases and to any genotype selected from the group consisting of 87R/87R, FcαRIA 92D/92N, FcαRIa 132F/132L, FcαRI 245P/245L and FcαRI 248S/248G.

Applicant should note that while method steps including the detection of SNPs is enabled, the use of these SNPs is not. While applicant points to page 11 in their specification to provide the examiner with the "how to use" basis for the enablement requirement, the examiner does not find this citation to be convincing. The specification lacks a teaching of how to use the FcαRI genotype in any correlation to disease. Applicant's further citation of the specification at pages 6 and 7 points examiner to data involving FcgammaRI and IgG. Applicant is reminded of the unequivalence established between these two molecules and those that are claimed in the prior final action. As a result, applicants arguments concerning the availability of understanding relating to how the IgA binding relates to cell genotype and therefore to disease to be unconvincing. In response to applicant's comments regarding basic immunology, as stated above just because a part of an invention or a method step is enabled by the art does not mean that the entire invention encompassing some of these enabled steps is enabled. Applicant should also note that the citation of case law in this response does not appear to make sense to the examiner. Lastly, the applicant's interpretation of the In re Wands factors is noted. However, the examiner does not find this interpretation to be convincing as she maintains the enablement analysis constructed in her previous two actions sent to applicant.

While the examiner acknowledges applicants assertions, her test whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors, and in this present invention proved to warrant, and now maintain, a rejection under 35 U.S.C 112 First Paragraph.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sally Sakelaris
5/4/2004

JEFFREY FREDMAN
PRIMARY EXAMINER
5/4/04